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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/538,248	03/29/2000	David A. Cheresh	TSRI-651.3	6166

2387 7590 08/23/2005

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/538,248	CHERESH ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,17-20,32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,17-20,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/04 has been entered.

Claims 5-16 and 21-31 have been canceled. Claims 1-4, 17-20 32 and 33 are still at issue and are present for examination.

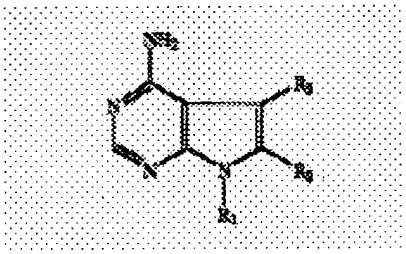
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 17, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Calderwood et al. (US Patent 6,001,839).

Calderwood et al. teach methods of treating diseases including VEGF mediated edema using tyrosine kinase inhibitors

having the structure shown below (see column 13, lines 29-48).



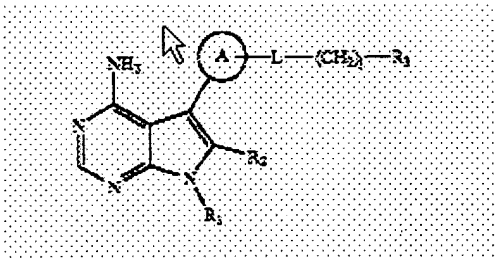
These compounds are disclosed as inhibitors of tyrosine kinases including Src kinases (see column 12 line 53 - column 13, line 10). Calderwood et al. further teach pharmaceutical compositions of the disclosed compounds. Thus Calderwood et al. anticipate all of the instant claims.

Applicants argue that the Calderwood et al. patent teaches that certain pyrrolopyrimidine compounds are useful for treating VEGF mediated edema but does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-src. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivity and activity depending on the spatial arrangement of substituents. This is not persuasive because Calderwood et al. clearly teach the use of each of the specific compounds listed in columns 7-10 for the treatment of VEGF-mediated edema and as the patent teaches the specific structures of these compounds as well as methods of making them the methods disclosed are unquestionably enabled. This list includes the specific compounds 7-isopropyl-5-(4-

phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, (column 9, lines 7-8), 5-[4-(4-aminophenoxy)phenyl]-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (column 9, lines 32-33), and 5-[4-(3-aminophenoxy)phenyl]-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (column 9, lines 34-35), which Burchat et al. (2000) evidence are src kinase inhibitors (see Table 2). Applicants statement that Burchat et al. does not show inhibition of c-src is not understood as Table 2 of Burchat et al. is clearly an assay of the ability of the recited compounds to inhibit a variety of Src family members including src.

Claims 1, 2, 17, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Calderwood et al. (US Patent Application 2003/0187001).

Calderwood et al. teach methods of treating diseases including VEGF mediated edema using tyrosine kinase inhibitors having the structure shown below (see paragraph 56 and 101).



These compounds are disclosed as inhibitors of tyrosine kinases including Src kinases (see paragraphs 53 and 111). Calderwood et al. further teach pharmaceutical compositions of the

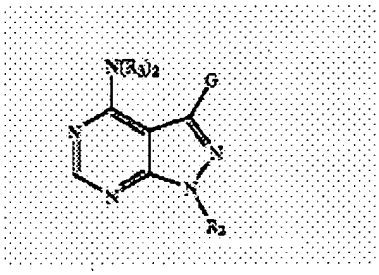
disclosed compounds. Thus Calderwood et al. anticipate all of the instant claims.

Applicants argue that the Calderwood et al. application teaches that certain pyrrolopyrimidine compounds are useful for treating VEGF mediated edema but does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-src. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivity and activity depending on the spatial arrangement of substituents. This is not persuasive because Calderwood et al. clearly teach the use of each of the specific compounds disclosed for the treatment of VEGF-mediated edema and as the application teaches the specific structures of these compounds as well as methods of making them the methods disclosed are unquestionably enabled. This specifically disclosed compounds include 4-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzyl Alcohol, (paragraph 0482), 2-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzyl Alcohol (paragraph 0495), 4-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile (paragraph 0439) and 2-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile (paragraph 0447), which Burchat et al. (2000) evidence are src kinase inhibitors (see Table 2). Applicants statement that

Burchat et al. does not show inhibition of c-src is not understood as Table 2 of Burchat et al. is clearly an assay of the ability of the recited compounds to inhibit a variety of Src family members including src.

Claims 1, 2, 17, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Hirst et al. (US Patent Application 2002/0156081).

Hirst et al. teach methods of treating diseases including edema using tyrosine kinase inhibitors having the structure shown below (see paragraph 315 and 350).



These compounds are disclosed as inhibitors of tyrosine kinases including Src kinases (see paragraphs 311 and 349). Hirst et al. further teach pharmaceutical compositions of the disclosed compounds. Thus Hirst et al. anticipate all of the instant claims. While the effective filing date of Hirst et al. (9/17/99) falls after some of the claimed priority dates of the instant application, none of the claimed prior applications teach the use of small organic chemical inhibitors of Src family tyrosine kinases for treatment of conditions related to vascular

leakage or edema and neither PCT/US99/11780 nor provisional application 60/087,220 provide support for treatment of conditions related to vascular leakage or edema as is currently claimed. As such the instant claims have not been granted the benefit of the filing date of the prior applications.

Applicants argue that Hirst et al does not provide an enabling disclosure of the presently claimed invention. Applicants argue that treatment of edema is discussed only generally in a laundry list of conditions in paragraph 315 of Hirst et al. and that the application states only that some of the compounds can be used to treat edema. Applicants argue that of the over 950 examples of compounds presented in Hirst et al. there is not a single data point of inhibition data. Only general allusions to unspecific activity against various diverse classes of tyrosine kinases is provided. This is not persuasive because despite the fact that treatment of edema is only one of several conditions to be treated, Hirst et al. clearly teach the use of each of the 982 compounds of examples 1-982 for the treatment of edema and teach how to make each of these specific compounds and thus the methods disclosed are unquestionably enabled. As such the use of each of these compounds is clearly enabled by Hirst et al. The examples include the specific compounds trans-Benzyl N-[4-[4-amino-1-[4-(4-

methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]carbamate (see paragraph 0686), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]benzamide (see paragraph 0697), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-2,2-dimethyl-3-phenylpropanamide (see paragraph 2549), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-3-methyl-3-phenylbutanamide (see paragraph 2562), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]benzo[b]furan-2-carboxamide, (see paragraph 2585), Trans-3-[4-(Benzylamino)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine, (see paragraph 0929) and trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-3-phenylpropanamide (see paragraph 1696) which Burchat et al. (2002) evidence are src kinase inhibitors (see Tables 3 and 4). Applicants statement that Burchat et al. (2002) has a date after the filing date of the present application and thus does not support the instant rejection is not persuasive. Burchat et al. (2002) was only used to evidence that the specific compounds disclosed by Hirst et al. inherently

are Src kinase inhibitors. Use of a later filed disclosure to show that a characteristic not disclosed in the reference is inherent in the prior art compound is proper (See MPEP 2131.01).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

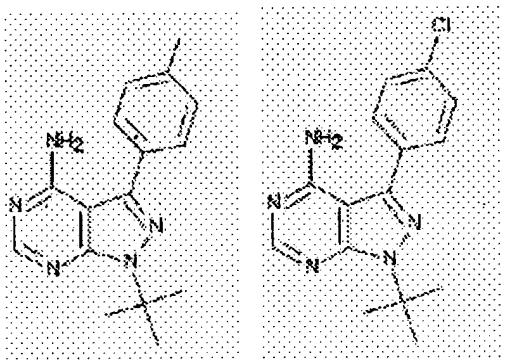
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 4, 19, 20, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calderwood et al (US Patent 6,001,839), Calderwood et al. (US Patent Application 2003/0187001) and Hirst et al. (US Patent Application 2002/0156081) in view of Hanke et al.

Calderwood et al (US Patent 6,001,839), Calderwood et al. (US Patent Application 2003/0187001) and Hirst et al. are all discussed above. Each of the above teach the treatment of edema

with tyrosine kinase inhibitors which inhibit tyrosine kinases including Src kinases. None of them specifically teach the use of the pyrazolopyrimidines PP1 or PP2 for the treatment of edema.

Hanke et al. teach the pyrazolopyrimidines PP1 and PP2 having the structures shown below.



PP1 PP2

Hanke teach that PP1 and PP2 are tyrosine kinase inhibitors which inhibit Src kinases. Hanke et al. do not teach the use of PP1 or PP2 to treat edema.

The structural similarity of PP1 and PP2 to the tyrosine kinase inhibitors of Calderwood et al (US Patent 6,001,839), Calderwood et al. (US Patent Application 2003/0187001) and Hirst et al. is readily apparent to a skilled artisan and these compounds are similarly disclosed as tyrosine kinase inhibitors which inhibit tyrosine kinases including Src kinases. As such it would have been obvious to one of skill in the art to use PP1

and PP2 to treat edema as taught by Calderwood et al (US Patent 6,001,839), Calderwood et al. (US Patent Application 2003/0187001) and Hirst et al. for the structurally and functionally similar tyrosine kinase inhibitors.

Applicants argue that the alleged structural similarity between the Calderwood compounds and PP1 and PP2 is superficial at best. The compounds of the Calderwood references are pyrrolopyrimidines, whereas PP1 and PP2 are pyrazolopyrimidines. The additional nitrogen in PP1 and PP2 relative to the Calderwood compounds could have a significant effect on activity and selectivity as inhibition of tyrosine kinases is highly unpredictable. In addition, the Calderwood compounds have a bulky phenoxy substituent on the phenyl ring, whereas PP1 and PP2 have relatively small methyl and chloro substituents on the phenyl ring. These differences could have significant effects on the selectivity as small changes in structure can lead to large changes in activity and selectivity. This is not persuasive as applicants arguments ignore the Hirst et al. reference entirely. The Hirst et al. reference teaches pyrazolopyrimidines and teaches the same utilities for these compounds as taught for the pyrrolopyrimidine compounds of the Calderwood et al. references. The similarities in structure are clear and as all the compounds are disclosed for the same utilities the skilled artisan would

believe other similar structures would have these same utilities. The similarity of the compounds PP1 and PP2 of Hanke et al., to the compounds of each of the three references, and in particular to the pyrazolopyrimidines of Hirst et al. is very clear. As such the skilled artisan would have a reasonable expectation that these compounds could be used in similar fashion. Applicants are reminded that obviousness does not require an absolute certainty of success but merely a reasonable expectation thereof. Furthermore, it should be noted that even if one were to conclude that there is not a reasonable expectation of treating edema with PP1 and PP2, the instant references would still make obvious claims 19, 20, and 32, as the combination clearly makes obvious a pharmaceutical composition of the Src kinase inhibitors of Hanke et al. for the treatment of cancer or osteoporosis as Hirst et al. clearly teach that Src kinase inhibitors are known to be useful for treatment of these conditions (see paragraph 0037). The intended use (as defined by the words on the label of Claims 19, 20, and 32) of a composition does not limit the composition itself. (see *In re Ngai*, 70 USPQ2d 1862). Applicants argue that Ngai is readily distinguishable. Applicants argue that the specific composition containing human c-src tyrosine kinase inhibitor and capable of modulating vascular permeability

increase as defined by these claims is not in the prior art and neither is a packaged version of that composition as claimed. The argument is not understood. Hanke et al. unquestionably teaches compositions of PP1 and PP2. There is no difference between the compositions of PP1 and PP2 of Hanke et al. and those of the instant claims. Furthermore, the inclusion of a pharmaceutical composition in a package with printed material is well known in the art and does not define a patentable feature of the composition. What the printed matter states cannot define the invention. While a new use for an old compound may be patentable the compound itself is not.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

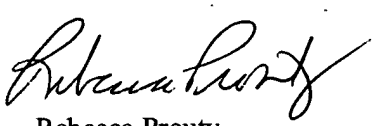
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this

action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Rebecca Prouty
Primary Examiner
Art Unit 1652